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Subglottic Secretion Drainage to Prevent Ventilator-Associated Pneumonia in Mechanically Ventilated Adult Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Patients requiring invasive mechanical ventilation in the intensive care unit (ICU) are at risk for ventilator-associated pneumonia (VAP).
Objectives: To summarize the results of published, randomized, clinical trials (RCTs), a meta-analysis was performed to examine the effect of subglottic secretion drainage (SSD) on the prevalence and outcomes of VAP in adult patients undergoing mechanical ventilation.
Methods: A comprehensive search based on specific terms was performed as a systematic review and meta-analysis by a computerized database search in the national and international databases including MagIran, SID, Scopus, PubMed, ISI Web of Knowledge, ScienceDirect, Google Scholar, Cochrane Central, and IRCT as well as references from 1990 to 2018 in English and Persian languages. RCTs of SSD were considered as common care of adult patients undergoing mechanical ventilation in the current meta-analysis. Data analysis was carried out through the random and fixed effects model, and the heterogeneity was investigated by I2 and Q-Cochrane index. The data were analyzed using STATA 11.
Results: A total of 24 eligible RCTs with 2434 patients were identified. The overall risk ratio for VAP was 14.7 (95% confidence interval (CI): 11.1 - 18.4); mortality 25.8 (95% CI: 17.3 - 34.3); length of ICU stay 13.4 (95% CI: 7.8 - 18.9) and hospital stay 23.2 (95% CI: 12.5 - 33.9); ventilation days 14.9 (95% CI: 7.3 - 22.6); airway secretion 10.2 (95% CI: 4.9 - 15.5); and APACHEII 19.5 (95% CI: 14.6 - 24.3).
Conclusions: SSD is recommended to prevent VAP, and reduce mortality rate and the ICU LOS, especially in the high-risk patients undergoing mechanical ventilation for a long period of time.

Keywords: Intensive Care Unit, Lengths of Stay, Mechanical Ventilation, Subgluttic Secretion Drainage, Suctioning, Ventilation-associated Pneumonia

1. Background

The risk for ventilator-associated pneumonia (VAP) is high in patients requiring invasive mechanical ventilation (MV) (1). The rate of VAP is 1 - 53 cases per 1000 ventilator days in European and North American ICU (intensive care unit) settings (2). VAP occurs in 9% - 35.4% of patients receiving MV (3, 4). The mortality rate of VAP is estimated 9% - 76% (2-4).

Prolonged length of hospital stay (LOS) and ICU stay are attributed to VAP incidence and can cause increased healthcare costs (5-7) and antibiotic consumption (8, 9).

The microaspiration of pathogenic microorganisms from the upper respiratory tract (trachea and oropharynx) secretions is a primary mechanism of VAP; due to impairment of laryngeal function by the endotracheal tube (ETT), mechanically ventilated patients are at a very high risk for microaspiration (10).

Hand hygiene, oral care with chlorhexidine, maintaining the head elevated tilt position, monitoring, and isolation measures are made to reduce the risk of cross-contamination with resistant bacteria; in addition, use of

specially designed ETT and attempting the subglottic secretion drainage (SSD) are considered as VAP prevention strategies to reduce the risk of VAP in patients admitted to ICU (8, 11); therefore, use of SSD, conical cuff shape, and continuous control of tracheal cuff pressure are the preventive measures for microaspiration and VAP (12).

Several published studies declared that SSD was associated with a lower rate of VAP, but the effect of SSD on the incidence of late-onset VAP, duration of MV, and ICU or hospital LOS is unclear. The results of several randomized, controlled trials (RCTs) investigated the effect of SSD on VAP were inconclusive and summarized in some meta-analyses (13-18); however, systematic reviews and meta-analyses reported no significant differences between continuous and intermittent SSD in terms of the treatment outcomes (19). However, previous meta-analyses reported that SSD decreased the risk of VAP (13-18), duration of MV (13-16, 18), delayed VAP onset (15, 18), and ICU LOS (13, 16). According to the results of some meta-analyses, comparison of the SSD and control groups showed no reduction in ICU or hospital mortality rate (13-16, 18), the incidence of late-onset VAP, or ICU or hospital LOS (14, 15, 20). Although use of SSD may provide important benefits to patients, their families, and healthcare system, evidence show that SSD may not decrease the mortality rate as applying ETT with SSD imposes higher cost to the healthcare providers and may increase the airway resistance because of the narrowed inner lumen (15).

Therefore and despite the reported benefits of SSD in studies, this procedure is limited in clinical settings (17) and European consensus does not recommend SSD for VAP prevention (15). Therefore, it is necessary to conduct an umbrella review of systematic reviews and meta-analysis and update the studies to provide more strong evidence.

2. Objectives

To summarize the results of published RCTs, a meta-analysis was performed to examine the effect of SSD on the prevalence and outcomes of VAP in adult patients undergoing MV.

3. Methods

3.1. Protocol and Registration

In the current umbrella review and meta-analysis, critically ill patients receiving invasive MV or endotracheal intubation were included. No changes were made to the protocol after the start of the study. No registration was also available for the study.

3.2. Eligibility Criteria

The inclusion criteria were: patients $\geq$ 18 years old; receiving MV $\geq$ 48 hours; receiving SSD irrespective of intermittent or continuous form; patients diagnosed with VAP; studies with experimental design- i e, RCTs, with full text available in English or/and Persian languages. The English and Persian languages were selected due to authors' language capabilities. The exclusion criterion was the duplicate papers.

3.3. Information Sources

The electronic databases were searched from January 1990 to March 2018 by two researchers in English and Persian languages.

3.4. Search Strategy

The following keywords were used: "ventilator-associated pneumonia"; "subglottic secretion" or "subglottic drainage" or "subglottic suctioning" or "glottic"; and "randomized" or "randomised"; moreover, the reference list of conference proceedings and review articles were searched manually. For computerized literature search, different electronic databases were included by focusing on MagIran (http://www.magiran.com/), SID (http://www.sid.ir/), Google Scholar (http://scholar.google.com), Scopus (www.elsevier.com/solutions/scopus), ISI Web of Knowledge (http://www.isiwebofknowledge.com), ScienceDirect (www.sciencedirect.com), PubMed (www.ncbi.nlm.nih.gov./entrez/query.fcgi), CENTRAL (Cochrane Central Register of Controlled Trials, (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.htm), and IRCT (http://www.irct.ir/). For unpublished trials, the investigators searched the clinical trial registers, conference proceedings, and graduate dissertations; in addition, researchers corresponded through email with some authors. The syntax of Scopus, PubMed, and ISI Web of Knowledge were available on Scopus: (TITLE-ABS-KEY ("ventilator-associated pneumonia" OR "subglottic secretion" OR "subglottic drainage" OR "subglottic suctioning" OR "glottis") AND TITLE-ABS-KEY ("randomized" OR "randomized"); PubMed: ("ventilator-associated pneumonia" [Title/Abstract] OR "subglottic secretion" [Title/Abstract] OR "subglottic drainage" [Title/Abstract] OR "subglottic suctioning" [Title/Abstract] OR "glottis" [Title/Abstract]) AND ("randomized" [Title/Abstract] OR "randomized" [Title/Abstract]); Web of Science: TOPIC: ("ventilator-associated pneumonia" OR "subglottic secretion" OR "subglottic drainage" OR

"subglottic suctioning" OR "glottis") AND TOPIC: ("randomized" OR "randomised").

3.5. Relevant Studies Quality Assessment

Critical appraisal (CA) was performed by applying the evidence-based library (EBL) critical appraisal checklist (21) by two researchers. The EBLCA checklist includes the calculations for the validity of the studies. Population, data collection, study design, and results are the four main categories of the checklist employed. Items are answered by choosing each of the Yes, No, Unclear, or Not Applicable options. According to the CA checklist, if number of yes/total was less than 75% or if number of no plus unclear/total was higher than 25%, significant omissions of the part could be deduced and the validity of the study was questionable. Overall validity (number of yes plus no plus unclear answers should be equal to total) calculation was similar to the part's validity, if number of yes/total was $\geq$ 75% or if number of no plus unclear/total was $\leq$ 25%, the validity of study could be confirmed (22).

In the current study, justification and training about the questions on checklist were carried out in a common meeting before performing CA. The purpose of the meeting was to train and pilot the CA. CA was performed for all 24 studies. In case of any disagreement for the CA scores between the researchers, the issue was rechecked by the third party. The low-quality papers were excluded from the analysis/final report (Figure 1).

3.6. Data Extraction

Using a standard checklist, data extraction was carried out by two researchers independently for each included study. Definition of VAP, mortality rate based on the duration of MV, detection rate of bacteria in airway secretions, ICU LOS, the incidence of VAP, the number of patients, year of publication, patients characteristics, and details of the outcomes were collected for each study.

3.7. Data Collection Process

The review process was initially commenced by two researchers. Titles and abstracts of the potentially relevant articles were examined according to the described search strategy. Two researchers independently screened the titles and abstracts using a predefined extraction sheet. Full texts of the selected papers were precisely investigated to identify the eligible studies. In case of similar cases, the study with more available relevant data was enrolled. The quality assessment was finally performed for each study by two experts, independently. Then in a meeting, excluded and included studies were discussed. The Kappa statistic (Inter-rater agreement) between the two researchers was 0.93.

3.8. Summary Measures

Summary of the prevalence of three outcomes as ICU mortality rate, hospital mortality rate, and VAP incidence in the groups with and without SSD was measured. First, the included studies were sorted according to the publication year and then a cumulative meta-analysis was run.

3.9. Synthesis of Results

The random-or-fixed effects model was used in the current study. Heterogeneity between studies was tested by means of Cochran Q (chi-square, N-1 degrees of freedom) and the I^2 statistic using $P < 0.05$ to indicate heterogeneity. Random-or-fixed effects model was used for the meta-analysis according to the result of heterogeneity tests, by means of the metan command in STATA 11 software (STATA Corp., LP). To determine the statin effects according to the DerSimonian and Laird approach, pooled hazard ratios (HR) and its 95% confidence interval (CI) were also calculated.

4. Results

4.1. Study Selection

In the current umbrella review and meta-analysis, 24 studies with 2434 patients were identified. In addition, 6750 references were identified and 1400 studies were also selected for a secondary review; finally, 24 papers met the inclusion criteria and were enrolled in the meta-analysis.

The inclusion criterion was reporting one of the following items in the study:

Duration of expected MV, incidence of VAP, mortality rate, hospital or ICU LOS (Figure 1).

4.2. Study Characteristics

Clinical and microbiological criteria along with new or persistent pulmonary infiltrates on a chest radiograph were considered for the VAP definition (23). Table 1 demonstrates the publication year of studies, inclusion criteria, sample size, VAP prevalence, mortality rate, and the ICU LOS of patients in the selected studies. Eighteen studies were included in the analysis of VAP incidence.

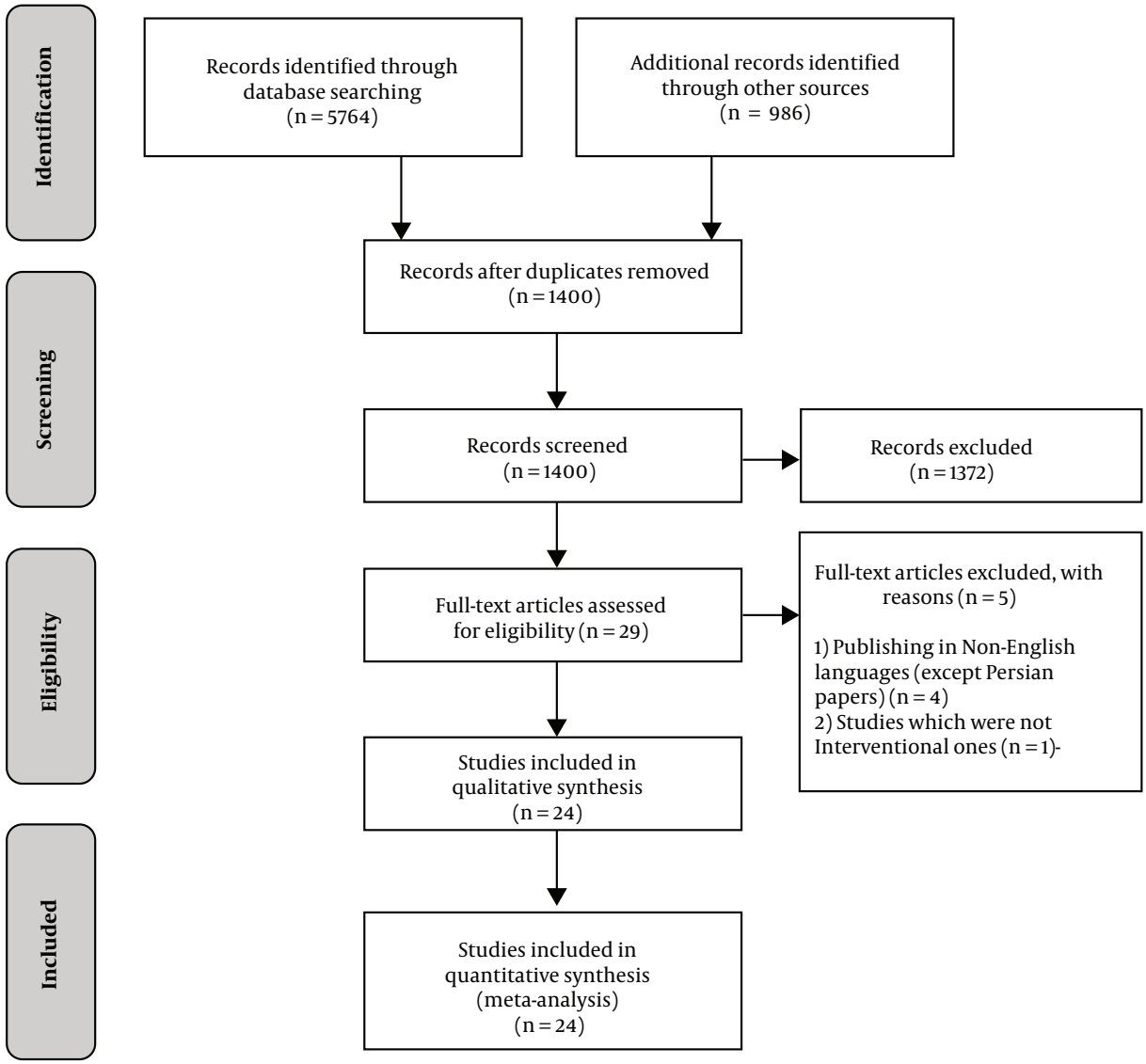

Figure 1. Flow chart of the study selection

4.3. Publication Bias

Meta-analysis of VAP and mortality rate in all included studies showed a significant publication bias (Table 2 and Figure 2). The Egger regression asymmetry analysis showed a significant publication bias for VAP ($P < 0.0001$) and mortality rate ($P = 0.003$) (Figure 2). To ensure the accuracy of the results, the sensitivity analysis was used to exclude each study and obtain a pooled estimate of the effects of VAP, mortality rate, and LOS (Figure 3). According to Figure 3, the results of sensitivity analysis showed that none of the studies alone had a significant impact on the pooled effect size estimation of the VAP, mortality rate, and ICU LOS variables.

4.4. Results of Individual Studies

The results of two studies reporting the mean mechanical ventilation (MMV) could be aggregated; likewise, MMV duration was 14.9 days (95% CI: 7.3 - 22.6) (Table 2) and there was a heterogeneity ($P = 0.016$, $I^2 = 82.9\%$). The detection rate of bacteria in airway secretions reported only in two RTCs was 10.2% (95% CI: 4.9 - 15.5) with no heterogeneity ($P = 0.141$, $I^2 = 53.9\%$) (Table 2). Seven studies had mentioned

Table 1. Characteristics of Eligible Studies and VAP Outcomes

First Author	Year	Inclusion Criteria	Sample Size	Age, y Mean ± SD	Male, N (%)	VAP Prevalence (95% CI)	Mortality Rate, (95% CI)	ICU LOS (d)	Quality
Fujimoto (24)	2018	NA	16	70.9 ± 8.9	10 (62.5)	0.44 (0.23 - 0.67)	0.12 (0.03 - 0.35)	9.8 (7.45 - 12.15)	Moderate
Mahmoodpoor (25)	2017	Mechanically ventilated patients < 72 h	138	54.5 ± 18.1	102 (72.3)	0.22 (0.16 - 0.29)	0.27 (0.21 - 0.35)	15.0 (14.17 - 15.83)	Low
Akdogan (26)	2017	Intubated < 48 h from ICU admission	37	60.32 ± 21.55	28 (75.68)	NA	0.78 (0.21 - 2.06)	23.7 (15.86 - 31.54)	Moderate
Hubbard (27)	2016	Adult trauma patients orotracheally intubated < 48 h	468	45 ± 20	368 (79)	0.07 (0.05 - 0.10)	0.24 (0.20 - 0.28)	14.0 (12.82 - 15.18)	High
Deem (28)	2016	Criteria of the Center for Disease Control	102	55 ± 19	72 (70)	NA	NA	NA	Low
Damas (29)	2015	Clinical features and culture of ETA	170	66	107 (62.9)	0.22 (0.17 - 0.29)	0.46 (0.39 - 0.53)	NA	Moderate
Safdari (30)	2014	NA	38	42 ± 14.66	27 (71)	0.24 (0.13 - 0.39)	NA	NA	Low
Koker (31)	2014	NA	NA	NA	NA	NA	NA	NA	Low
Gopal (32)	2015	Europe Infection Control through Surveillance definition	120	72.4 ± 8.2	NA	0.11 (0.07 - 0.18)	0.02 (0.01 - 0.06)	NA	Moderate
Tao (33)	2014	Received MV > 48 h, clinical features and culture of ETA; reduction of blood oxygen	149	NA	NA	0.28 (0.21 - 0.35)	NA	NA	Moderate
Seyfi (34)	2013	NA	40	59.59 ± 17.14	NA	0.11 (0.04 - 0.24)	NA	NA	Low
Lacherade (35)	2010	Quantitative culture of protected telescoping catheter samples or bronchoalveolar lavage fluid following clinical suspicion	169	NA	101 (59.8)	0.15 (0.10 - 0.21)	0.47 (0.40 - 0.55)	NA	High
Zheng (36)	2008	NA	30	NA	NA	0.30 (0.17 - 0.48)	0.27 (0.14 - 0.44)	9.3 (8.26 - 10.34)	High
Yang (37)	2008	Clinical features and culture of ETA	48	NA	NA	0.25 (0.15 - 0.39)	NA	NA	Moderate
Bouza (38)	2008	Received MV > 48 h, clinical features, and culture of ETA; reduction of blood oxygen	331	65.7 ± 11.9	191	0.04 (0.03 - 0.06)	0.07 (0.05 - 0.1)	NA	Moderate
Lorente (39)	2007	Clinical features and significant quantitative culture via ETT aspiration	140	60.0 ± 16.79	NA	0.08 (0.04 - 0.14)	0.23 (0.17 - 0.31)	15.5 (12.2 - 18.8)	Moderate
Liu (40)	2006	Received MV > 48 h, clinical features, and culture of ETA; reduction of blood oxygen	41	NA	NA	NA	NA	NA	Low
Liu (41)	2006	MV > 48 h, the chest X-ray showed pulmonary new or progressive infiltration lesions, and excluding atelectasis, pulmonary edema, and pleural effusion	NA	NA	NA	NA	NA	NA	Moderate
Girou (42)	2004	Clinical features and significant quantitative culture of aspiration	8	NA	5 (62.5)	NA	NA	NA	Low
Smulders (43)	2002	Clinical features or positive blood/pleural cultures	75	63.7 ± 13.2	42 (56)	0.04 (0.01 - 0.11)	0.16 (0.09 - 0.26)	9.3 (7.36 - 10.97)	Moderate
Bo (44)	2000	Clinical features or positive blood/pleural cultures	35	NA	NA	0.23 (0.12 - 0.39)	NA	NA	Moderate
Kollef (45)	1999	Clinical features, positive tracheal, blood, or pleural cultures; radiographic abscess, or positive histology	160	64.7 ± 12.3	102	0.05 (0.03 - 0.10)	0.04 (0.02 - 0.08)	3.7 (2.99 - 4.41)	High
Valles (46)	1995	Clinical features confirmed with bronchoscopically obtained cultures	76	62.9 ± 16.7	54	0.18 (0.11 - 0.29)	0.24 (0.14 - 0.35)	22.0 (21.55 - 22.45)	Moderate
Mahul (47)	1992	Positive culture of the bronchoalveolar lavage fluid	145	NA	NA	0.13 (0.11 - 0.20)	NA	NA	Moderate

Abbreviations: CI, confidence interval; ETA, endotracheal aspirate; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; NA, not available; SSD, subglottic secretion drainage; VAP, Ventilator-associated pneumonia.

the APACHI score of patients with SSD as 19.5 (95% CI: 14.6 - 24.3) with heterogeneity ($P < 0.0001$, $I^2 = 99.2\%$) (Table 2).

4.5. Synthesis of Results

In the meta-analysis, the primary outcome was the VAP incidence, the overall prevalence of VAP was 14.7 (95% CI: 11.1 - 18.4) with heterogeneity ($P < 0.0001$, $I^2 = 87.6\%$) (Table 2 and Figure 4). Pooled prevalence of mortality rate (ICU or hospital) reported in 13 papers was 25.8 (95% CI: 17.3 - 34.3, $P < 0.0001$) with heterogeneity ($P < 0.0001$, $I^2 = 97.1\%$) (Table 2 and Figure 5). The ICU LOS reported in 13 studies was 13.4 days (95% CI: 7.8 - 18.9) with heterogeneity ($P < 0.0001$, $I^2 = 99.6\%$) (Table 2). In addition, seven studies mentioned the mean of hospital LOS. The overall hospital LOS was 23.2

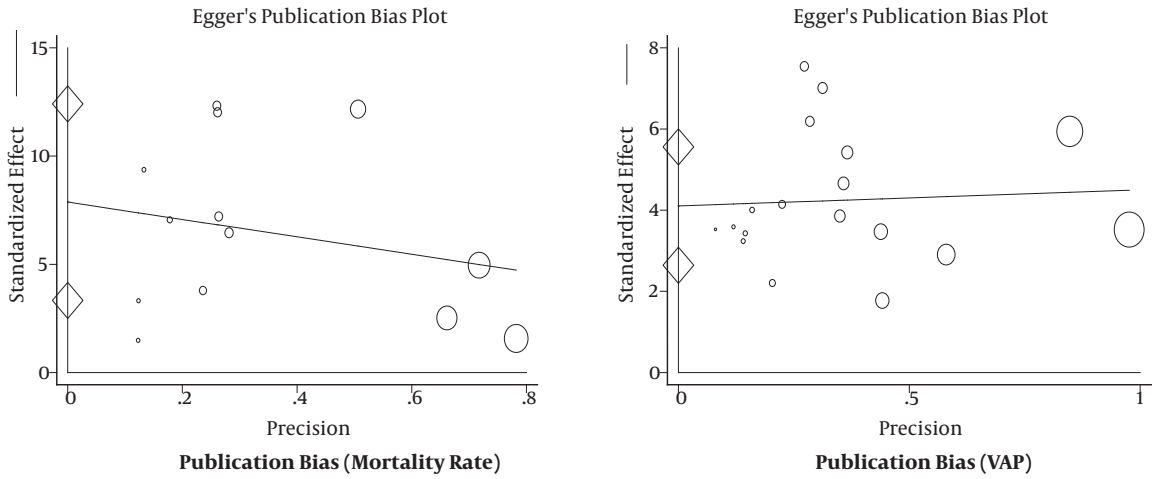

Figure 2. Publication bias in the studied papers; circles show the weight of studies

days (95% CI: 12.5 - 33.9) with heterogeneity ($P < 0.0001$, $I^2 = 98.7\%$) (Table 2).

5. Discussion

5.1. Summary of Evidence

Pooled information from published studies of the effect of SSD on the prevalence of VAP in mechanically ventilated adult patients admitted to ICU was conducted in the current meta-analysis. The study found that SSD significantly reduced the incidence of VAP in all entered studies. Likewise, previous meta-analyses reported that SSD decreased VAP incidence (13-18).

In the current study, mortality risk reduction was observed. In contrast, some meta-analyses reported no benefits in terms of reduced ICU or hospital mortality rate (13-16, 18, 48). Also, the present study showed that SSD could shorten the hospital and/or ICU LOS.

Similar to the current study, some meta-analyses reported that use of SSD decreased ICU LOS (13, 16). In contrary, some previous meta-analyses showed that in comparison of the SSD and control groups, no reduction in ICU or hospital LOS was observed (14, 15).

Also, in the current meta-analysis, a slight reduction was observed in days of MV. In fact, the authors found that SSD appears to reduce ventilation duration by about two days in patients who required MV for at least 48 hours. In this regard, several meta-analyses reported that SSD decreased the duration of MV (13-16, 18). For instance, the meta-analysis by Dezfulian et al. also showed that the duration of ventilation reduced by about two days when comparing the intervention and control groups (48).

Also, the current meta-analysis confirmed that SSD further reduced the detection rate of bacteria in airway secretions. A recently updated meta-analysis confirmed that SSD reduced the detection rate of bacteria in airway secretions (15).

Differences between the present and previous meta-analyses are as follows: First, the current meta-analysis included four additional studies (3, 24-26) published recently, and were not included in previous meta-analyses. As the latest and most comprehensively updated meta-analysis, the present study further reinforced the results of previous meta-analyses. Second, the researchers only considered patients who needed ETT with SSD.

5.2. Limitations

Potential limitations of the current meta-analysis were that the eligible RTCs enrolled in the present study included patients with different diagnoses and clinical settings. Also, only RTCs in English and Persian languages were included. Thus, the generalizability of the findings was questionable. Also, any future studies to assess the benefits of SSD in all mechanically ventilated patients may require a sample size of at least 4000 patients in each group (based on the VAP rate in the control group of the study by Kollef et al.) (45).

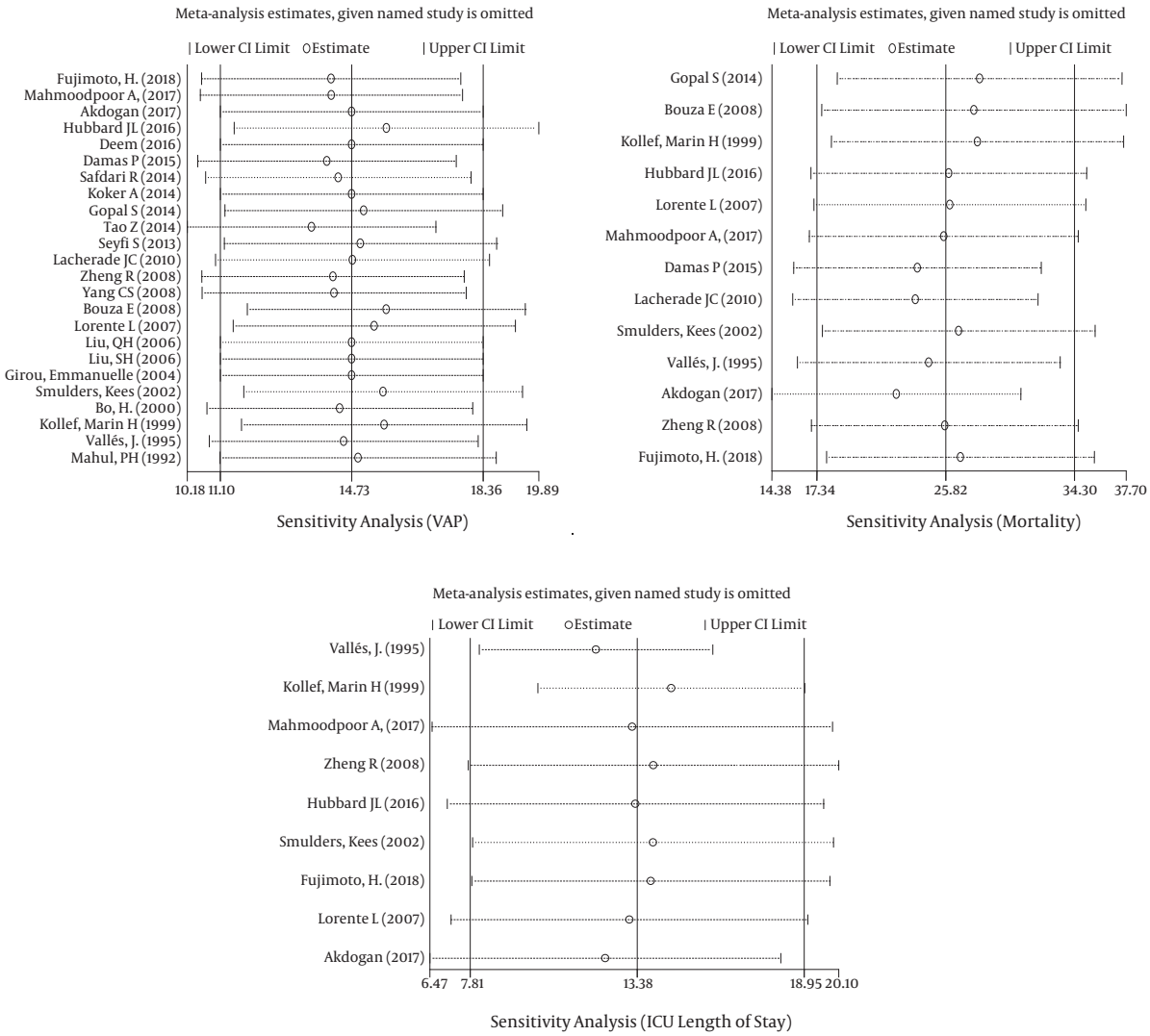

Figure 3. Sensitivity analysis for the VAP, mortality rate, and length of ICU stay

5.3. Conclusions

The current meta-analysis suggested that SSD significantly reduced the prevalence of VAP, mortality rate, the ICU and/or hospital LOS, hospitalization time, duration of MV, and detection rate of bacteria in airway secretions. In summary, SSD is recommended to reduce the risk of VAP and its outcomes.

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Footnotes

Authors' Contribution: Farshid Rahimibashar and Amir Vahedian-Azimi: the study concept and design, analysis and interpretation of data, drafting and critical revising of the manuscript. Zahra Farsi, Zahra Danial, and Sahar Dalvand: interpretation of data, drafting and critical revising

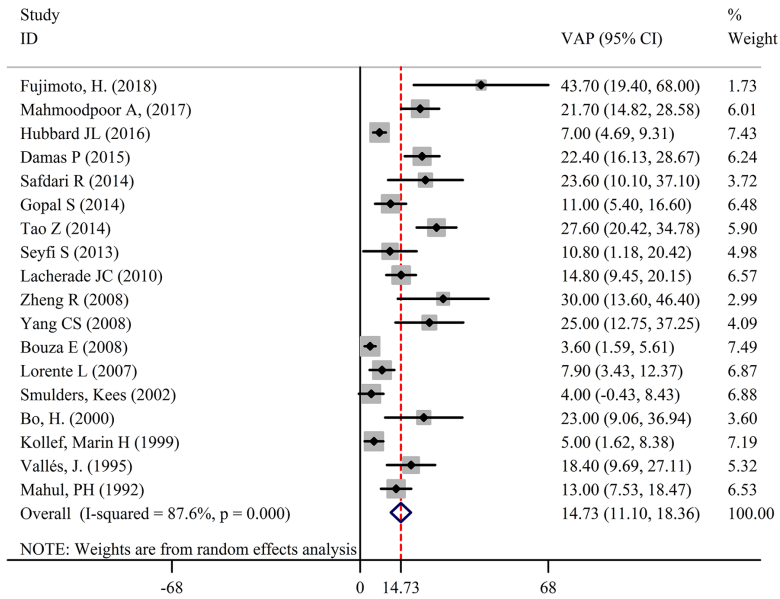

Figure 4. Forest plot of VAP prevalence in mechanically ventilated patients in the intensive care unit. The 95% confidence interval for each study is shown as horizontal lines around the mean; dotted lines in the middle indicate total mean score, and diamonds show the prevalence range of event.

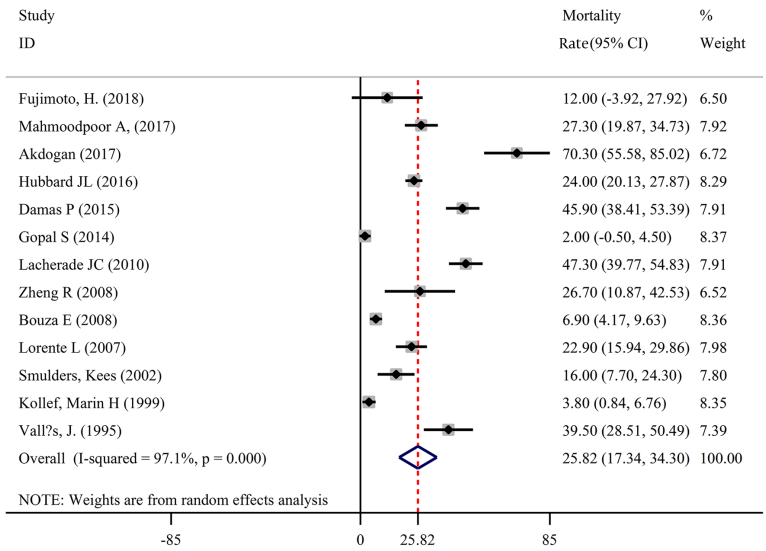

Figure 5. Forest plot of mortality rate in mechanically ventilated patients in the intensive care unit. The 95% confidence interval for each study is shown as horizontal lines around the mean; dotted lines in the middle indicate total mean score, and diamonds show the prevalence range of event.

of the manuscript. All authors read and approved the final manuscript.

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Table 2. Meta-analysis Results and Heterogeneity Information of the Studies Outcomes

Variable/Author, Publication Year	Effect Size (95% CI)	Pooled Effect Size (95% CI)	I^2%	Heterogeneity Test		Egger Test	
				Q	P Value	t	P Value
Length of ICU stay		13.4 (7.8 - 18.9)[a]	99.6	2078.6	< 0.0001	0.98	0.357
Fujimoto, 2018	9.8 (7.45 - 12.15)						
Mahmoodpoor, 2017	15.0 (14.17 - 15.83)						
Akdogan, 2017	23.7 (15.86 - 31.54)						
Hubbard, 2016	14.0 (12.82 - 15.18)						
Zheng, 2008	9.3 (8.26 - 10.34)						
Lorente, 2007	15.5 (12.20 - 18.8)						
Smuulders, 2002	9.30 (7 - 63 - 10.98)						
Kollef, 1990	3.7 (2.99 - 4.41)						
Valles, 1995	22.0(21.55 - 22.45)						
Ventilation days		14.9 (7.3 - 22.6)[a]	82.9	5.8	0.016	-	-
Mahmoodpoor, 2017	11.6 (10.42 - 12.79)						
Akdogan, 2017	19.5 (13.21 - 25.81)						
Mortality		25.8 (17.3 - 34.3)[a]	97.1	418.3	< 0.0001	3.82	0.003
Fujimoto, 2018	12 (- 3.9 - 12.9)						
Mahmoodpoor, 2017	27.3 (19.8 - 34.7)						
Akdogan, 2017	70.3 (55.6 - 85.0)						
Hubbard, 2016	24.0 (20.1 - 27.8)						
Damas, 2015	45.9 (38.4 - 53.4)						
Gopal, 2014	2.0 (- 0.5 - 4.5)						
Lacherade, 2010	47.3 (39.7 - 54.8)						
Zheng, 2008	26.7 (10.8 - 42.5)						
Bouza, 2008	6.9 (4.2 - 9.6)						
Lorente, 2007	22.9 (15.9 - 29.8)						
Smulders, 2002	16.0 (7.7 - 24.3)						
Kollef, 1990	3.8 (0.8 - 6.7)						
Valles, 1995	39.5 (28.5 - 50.5)						
VAP		14.7 (11.1 - 18.4)[a]	87.6	137.4	< 0.0001	5.97	< 0.0001
Fujimoto, 2018	43.7 (19.4 - 68.0)						
Mahmoodpoor, 2017	21.7 (14.8 - 28.6)						
Hubbard, 2016	7.0 (4.7 - 9.3)						
Damas, 2015	22.4 (16.1 - 28.7)						
Safdari, 2014	23.6 (10.1 - 37.1)						
Gopal, 2014	11.0 (5.4 - 16.6)						
Tao, 2014	27.6 (20.4 - 34.8)						
Seyfi, 2013	10.8 (1.2 - 20.4)						

Lacherade, 2010	14.8 (9.4 - 20.1)						
Zheng, 2008	30.0 (13.6 - 46.4)						
Yang, 2008	25.0 (12.7 - 37.2)						
Bouza, 2008	3.6 (1.6 - 5.6)						
Lorente, 2007	7.9 (3.4 - 12.4)						
Smulders, 2002	4.0 (- 0.4 - 8.4)						
Bo, 2000	23.0 (9.1 - 36.9)						
Kollef, 1990	5.0 (1.6 - 8.4)						
Valles, 1995	18.4 (9.7 - 27.1)						
Mahul, 1992	13.0 (7.5 - 18.5)						
Airway secretion		10.2 (4.9 - 15.5)[b]	53.9	2.2	0.141	-	-
Mahmoodpoor, 2017	13.2 (7.55 - 18.85)						
Lorente, 2007	7.8 (3.36 - 12.24)						
APACHEII		19.5 (14.6 - 24.3)[a]	99.2	778.0	< 0.0001	1.96	0.108
Fujimoto, 2018	14.8 (12.9 - 16.7)						
Mahmoodpoor, 2017	22.6 (21.7 - 23.5)						
Akdogari, 2017	29.3 (27.3 - 31.4)						
Lorente, 2007	15.1 (14.1 - 16.1)						
Smulders, 2002	23.1 (21.4 - 24.8)						
Kollef, 1990	11.1 (10.5 - 11.7)						
Valles, 1995	20.5 (18.9 - 22.1)						
Hospitalization time		23.2 (12.5 - 33.9)[a]	98.7	235.7	< 0.0001	0.13	0.906
Mahmoodpoor, 2017	27.2 (26.1 - 28.4)						
Akdogan, 2017	28.5 (20.8 - 36.3)						
Smulders, 2002	26.8 (21.5 - 32.1)						
Kollef, 1990	11.0 (9.3 - 12.7)						

[a] Random effects model.
[b] Fixed effects model.